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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/597,604	06/20/2000	Joseph R. Moskal	97,186-D	6352

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/597,604	MOSKAL ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,8,11,12 and 21-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8,11,12 and 21-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 08/24/03 has been acknowledged.

Claims 5-6, 9-10 and 13-20 are canceled.

Claims 22-32 are newly filed.

Claims 1-4, 7-8 and 11-12 are amended.

Claims 1-4, 7-8, 11-12, 21-32 are pending and are examined in this office action.

► *Applicants are required to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm).* The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Election/Restrictions

The restriction/election wherein the elected species α2,6-ST glycosyltransferase has been maintained, since there are no allowable generic or linking claim for the same reasons of record as set forth in the earlier office action and as stated below.

Claim Rejections - 35 USC § 112

Claims 1-4, 7-8, 11-12 and 21-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the same reasons of record as set forth in the office action mailed on 02/27/03.

Response to arguments

Applicant argues that the specification provides considerable guidance to enable to one skill in the art to make and use the method for decreasing the tumorigenicity or malignancy of a brain cancer cell. Applicant argues that specification at pages 61-62 teaches the stereotactic injection of recombinant adenoviral vector comprising α2,6-ST glycosyltransferase into an established tumor into rat brains. In addition the specification teaches how to decrease tunorigenicity of brain cancer cells in human following the surgical resection of a tumor. Applicant further argues that the specification teaches the implantation of genetically engineered cells into a mouse resulting in decreased tumorigenicity of implanted cells (response page 10). Applicant concluded that based upon the teaching and examples, one skill in the art would have know how to alter the glycosyltransferase activity within cells such that the tumorigenicity or malignancy of the brain cancer would be decreased (response page 11). In response to the unpredictable nature of treatment of a cancer the applicant argues that it is not necessary that applicant enables a cure for brain cancer, since the invention as claimed only requires the decreased tumorigenicity and malignancy of brain cancer cells (response page 12). Furthermore, considering the state of gene therapy art the applicant argues that acceptance of gene therapy is demonstrated by the FDA approval of numerous clinical trials, therefore the instant invention as claimed would not require undue experimentation by those ordinary skill in art in view of guidance provided in the instant specification (response page 13).

However, this is found NOT persuasive because applicant's argument alone cannot take place of evidence lacking in the record (see In re Scarbrough 182 USPQ, (CCPA) 1979). The scope of the claims must bear a reasonable correlation with the scope of enablement (In re

Fisher, 166 USPQ 19 24 (CCPA 1970)). Approval of the FDA of a therapy for clinical trail has little relevance to the question of enablement until the trail is successfully conducted. Significantly less than 1/3 of medicines placed in clinical trail even succeed phase I trails, so that a compound is more likely to fail in FDA trails. Further the issue here is not about compounds in general but about gene therapy treatment. No gene therapy treatment or product has been approved by FDA.

Nature Of Invention: The present invention relates to a method of decreasing tumorigenicity or malignancy of a brain cell by altering the expression of a glycosyltransferase in a cell.

Breadth of Claims and Guidance Provided in the Specification: The scope of invention as claimed encompasses decreasing the tumorigenicity or malignancy of any type of brain cancers by altering the expression of any glycosyltransferases within brain cancer cells (in-vivo or in-vitro) using any means (e.g. chemicals, proteins and nucleic acid molecules). At best the specification teaches that intra-cranial transplantation of α2,6-ST/U-3T3MG glioma cells in a mouse formed no tumors as compared to α2,3-ST/U-3T3MG transfectents and U-3T3MG control cells (page 48, line 4-14, fig-21). In addition the specification proposed the use of Ad α2,6-ST59 in treating established tumors or in the prevention of brain tumors following surgical resection of tumor. However the disclosure falls short of providing any evidence that such a treatment would decrease the tumorigenicity and/or malignancy of any type of brain cancer in any animal (see page 60-62, example-8, 9).

State Of Art And Predictability: The state of art at the time of filing was such that the expression and role of glycosylgransferases in the cancer development not only depends upon

the type of organ but also depends upon the type of cancerous tissue in a particular organ. The role of each glycosyltransferase is distinct and is even specific to a tumor type of interest (see Yamamoto et al Can. Res. 61;6822-6829, 2001, Yamamoto et al J Neurochem. 68: 2566-2576, 1997; Kaneko et al Acta Neuropathol 91:284-292, 1996). In addition, the treatment of a cancer is considered highly unpredictable because various genetic and etiological factors govern the development of the cancer. (Kelloff et al, Eur. J. Cancer. 35(14):2031-2035, 1999, page 2032, col.2 para.3; page 2034, table-1). The cancer therapy clearly demands molecular, phenotypic and functional characterization of a particular tumor type that proves amenable to induce cancer amelioration in vivo. (Gomez-Navarro et al, Eur. J. Cancer. 35(6);867-885, 1999, page 868, table-1). Furthermore, the malignant gliomas remains poorly understood form of cancer suggesting that future treatment strategies would likely involve synergistic combinations of agents aimed at different pathways in the molecular pathogenesis of this type of cancer (Avgeropoulos et al The Oncologist 4:209-2224, 1999, page 220 col.2). In addition gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Recombinant DNA Advisory committee (RAC) also emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease.

(Touchette, page 7, col.3, para.3). In instant case the specification fails to disclose that increase of activity of α2,6-ST glycosyltransferase would decrease the tumorigenicity and/or malignancy of any type of brain cancer cells. Furthermore considering the fact that the treatment of malignant gliomas is highly unpredictable (see Avgeropoulos et al The Oncologist 4:209-2224, 1999) the specification fails to provide a single working example, wherein the administration of vector encoding the α2,6-ST glycosyltransferase results in decrease the tumorigenicity and/or malignancy of an established glioma in any animal model. Furthermore in-vitro transduction of a tumor cell line does not correlate to therapeutic delivery of α2,6-ST DNA in-vivo. Furthermore, the transplantation of previously transfected U373 MG/α2,6-ST cells in a mouse does not correlate to the invention as claimed because the method requires the transduction of therapeutic genes (glycosyltransferases) into brain cancer cells. In addition the specification falls short of providing any evidence that such a treatment would decrease the tumorigenicity and/or malignancy of any type of brain cancer in any animal (see page 60-62, example-8, 9). Applicant fails to provide any evidence in example 8 and 9 of the specification that would enable one skill in the art to exercise the invention as claimed without further undue amount of experimentation. Examples 8 and 9 are mere prophetic examples, since specification fails to disclose any data in support.

Quantity Of Experimentation Required: In instant case decreasing the tumorigenicity or malignancy of any type of brain cancer by altering the expression of glycosylation of any protein by altering the activity of any glycosyltransferase with in the cancer cell via any and all means is not considered routine in the art and without sufficient guidance how to modulate the activity of a specific glycosyltrasferase in context to a specific brain cancer type the experimentation left to

those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Furthermore, it is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (See Brenner v. Manson , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "*a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion*") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. Therefore, considering the unpredictability in the state of art and limited guidance provide in the specification one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Claims 1-4, 7-8, 11-12 and 21-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the same reasons of record as set forth in the office action mailed on 02/27/03.

Response to arguments

Applicant argues that based upon what is conventional or well know to one ordinary skill in the art, invention need not to be disclosed in detail. Applicant argues that the specification describes sufficient identifying characteristics of the claimed invention and the office fails to present an evidence why a person skill in the art would not recognize the disclosure that the applicants were not in the possession of invention as claimed.

However, this is found NOT persuasive because the scope of invention as claimed encompasses a method for decreasing the tumorigenicity or malignancy of brain cancer cell comprising increasing the activity of any glycosyltransferase of any brain cancer cell type using all means (e.g. chemicals, proteins and nucleic acid molecules). The courts have clearly stated that: a specification needs not to disclose what is well known in the art. See, e.g., Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1385, 231 USPQ 81, 94(Fed. Cir. 1986). However, that general off-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific material or of any of the conditions under which a process can be carried out, undue experimentation is required: there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. *It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".* Genentech Inc. V. Novo Nordisk A/s, 42 USPQ2d 1005 (CAFC 1997). Furthermore the disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly

when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In instant case the specification fails to disclose a method of decreasing tumorigenicity or malignancy of brain cancer cell (all types) by altering the expression of any glycosyltransferase (all glycosyltransferase) by administering any nucleic acid, exogenous protein or a chemical agent. Furthermore, the specification fails to disclose a single inducible promoter that regulates the glycosyltransferases gene expression. Considering the applicant's disclosure it is even unclear what is the agent used to regulate the expression of the inducible promoter as claimed. Thus, one skill in the art would conclude that applicant was not in the possession of the all the method for decreasing the tumorigenicity or malignancy of brain cancer cell (all types), which comprises altering the activity of all glycosyltransferase by all means.

Claims 1-4, 7-8, 11-12 and 21-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: by administering to said cell an exogenous DNA encoding for a glycosyltransferase.

Claim Rejections - 35 USC § 102

Claims 1-3, 7 and 21-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamamoto et al (Proc Annu Meet Am Assoc Cancer Res, 37:63, A436 March 1996) for the same reasons of record as set forth in the office action mailed on 02/27/03.

Response to arguments

Applicant argues that the cited art must provide an enabling disclosure (response, page 19). Applicant argues that cited art is a single paragraph abstract that does not provide any details. The applicant admits that Yamamoto teaches genetic transfection into human glioma cells, but insists that the cited art does not disclose the invention as claimed (response, page 20).

However, this is found NOT persuasive because the scope of invention as claimed encompasses a method of decreasing the tumorigenicity or malignancy of any type of brain cancers by altering the expression of any glycosyltransferases within brain cancer cells (in-vivo or in-vitro) using any means (e.g. chemicals, proteins and nucleic acid molecules). The scope of invention as claimed is not limited to in-vivo use. The cited art clearly teaches a method of decreasing tumor invasivity of human glioma cell in-vitro. The cited art further teaches that a2,6 sialyltransferase (a2,6-ST) gene transfection alters the integrin-mediated invasivity of the human glioma (U-373MG). The cited art further teaches that transfected glioma cells express a2,6-ST and a2,6-linked sialogycoprotein on their surface and show marked reduction in a3b1-integrin-mediated adhesion to the extra cellular matrix proteins, and tumor cell invasiveness in-vitro as compared to untransfected controls. The cited art concluded that changes in the terminal

sialylation have marked effect on a2b1-integrin-mediated glioma invasivity and suggested the use of this approach to alter invasivity of glioma cells by glycosyltransferase gene transfection (page 63 col.1 abstract #436).

In addition The MPEP clearly states that limitations appearing in the specification but not recited in the claim are not read into the claim. In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969). See also In re Zletz, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). Claims define the property rights provided by a patent, and thus require careful scrutiny. The goal of claim analysis is to identify the boundaries of the protection sought by the applicant and to understand how the claims relate to and define what the applicant has indicated is the invention. See *In re Hiniker Co., 150 F.3d 1362, 1369, 47 USPQ2d 1523, 1529 (Fed. Cir. 1998).* Furthermore, preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. *See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).* In addition, if the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. *See In re Casey, 152 USPQ 235 (CCPA 1967) and In re Otto, 136 USPQ 458, 459 (CCPA 1963).* Thus, given the broadest reasonable interpretation the invention as claimed encompasses a method of decreasing the tumorigenicity or malignancy of brain cancer cell in-vitro, thus the cited art clearly anticipate the invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
PATENT EXAMINER

JEFFREY FREDMAN
PRIMARY EXAMINER